Docket No. 141-490

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Lodin et al.

Serial No.: 11/093,742 Group Art Unit: 1611

Filed: March 30, 2005 Examiner: Welter, Rachael E.

For: **NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE DERIVATIVE**

New York, New York 10036
August 2, 2010

Via Electronic Filing System
Hon. Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF KAZUHIRO OKOCHI UNDER 37 C.F.R. § 1.132

Sir:

I, Kazuhiro Okochi, declare and state as follows:

1. I am currently employed by Takeda Pharmaceutical Company Limited, the co-owner of the above identified patent application, and I am one of the named inventors listed on the above identified patent application.

2. I am associate director and I am responsible for all aspects of technology assessment of pharmaceutical technology at Takeda Pharmaceutical Company Limited.

3. I received a master from the Kyoto University. A copy of my curriculum vitae is attached as Exhibit A.

4. I have read and understand United States Published Patent Application No. 2005/0226928. It is my understanding that this Published Patent Application Corresponds to the above-identified patent application.

5. I have also reviewed: WO 01/35940 (hereinafter "Lewis"); U.S. Patent No. 6,838,093 (hereinafter "Flanner") and U.S. Patent No. 5,948,440 (hereinafter "Arora").

6. It is my understanding that the Examiner has relied upon these references to reject the claims of the above captioned patent application.

5. It is my further understanding that the above-identified application currently contains the following claim:

47. A pharmaceutical dosage form comprising:

(a) an osmotic tablet comprising:

(i) a compressed tablet core comprising at least one pharmaceutically acceptable excipient and only one active drug that consists of metformin hydrochloride, and

(ii) a sustained release membrane surrounding the compressed tablet core wherein the metformin hydrochloride is released from the osmotic tablet so the peak plasma level of metformin is obtained about 6-12 hours after administration of the dosage form following a meal; and

(b) an immediate release layer surrounding the sustained release membrane of the osmotic tablet comprising pioglitazone hydrochloride and a low viscosity water soluble binder that exhibits a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 20°C;

wherein not less than 90% of the pioglitazone is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia 26, with Apparatus 1 at 100 rpm, 37°C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0 and the total amount of pioglitazone impurities selected from the group consisting of:

(i) (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-5-hydroxy-2,4-thiazolidinedione;

(ii) (z)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione;

(iii) (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-3-[2-(5-ethyl-2-pyridyl)ethyl]-2,4-thiazolidinedione;

(iv) (+/-)-ethyl-2-carbamoyltio-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl] propionate; and

(v) ethyl-3-p-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl-propionate

that are present in the dosage form are not more than 0.6% as determined by high performance liquid chromatography.

6. I have been asked to organize and review data related to the stability of pioglitazone hydrochloride in formulations where the pioglitazone hydrochloride has been applied as an immediate release layer to a sustained release membrane surrounding a metformin core. A summary of the formulations and data reviewed is attached hereto as Exhibit B.

7. The stability data for three separate formulations was reviewed during the preparation of the present declaration.

8. The first formulation (formulation A) reviewed was prepared in accordance with Example 7 of the present application and contained the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

9. The second formulation (formulation B) reviewed was prepared in accordance with Example 8 of the present application and contained the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	

Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.32 mg/tablet
Polyethylene Glycol 8000, NF	0.84 mg/tablet
Titanium Dioxide, USP	0.84 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

10. A third formulation (formulation C) reviewed was prepared with the following formulation:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Povidone, USP (Kollidon K-30))	3.0 mg/tablet
Lactose Monohydrate, NF	90.0 mg/tablet
Poloxamer 188, NF (Lutrol F-68)	15.00 mg/tablet
Sodium Starch Glycolate, NF	30.00 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.32 mg/tablet
Polyethylene Glycol 8000, NF	0.84 mg/tablet
Titanium Dioxide, USP	0.84 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

11. Formulations A-C were packed in a 100 cc high density polyethylene (HDPE) bottles containing one 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions

of 40°C and 75% relative humidity for 0.5 months, 1 month, 2 months and 3 months. After storage, the final tablets were tested for pioglitazone related compounds by high performance liquid chromatography (HPLC). The results of the test are summarized in the table below:

Formulation	Initial impurities	0.5 M	1 M	2 M	3 M
Formulation A	0.18%	0.18%	0.19%	0.16%	0.16%
Formulation B	0.15%	0.14%	0.18%	0.14%	0.18%
Formulation C	0.14%	0.19%	0.29%	0.43%	0.75%

12. As shown in the above table, Formulation C is unstable compared with Formulations A and B, which were prepared in accordance with Examples 7 and 8 of the present application. The total pioglitazone related impurities in Formulation C exceeded the upper claim limit of not more than 0.6% of pioglitazone related impurities.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements and like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

August 2, 2010
Dated

Kazuhiro Okochi
Kazuhiro Okochi

EXHIBIT A

Curriculum Vitae

Name: Kazuhiro Okochi

Date	Education
March 1987	Graduate College of Pharmacy, Kyoto University
March 1989	Master degree from Graduate School of Pharmaceutical Sciences, Kyoto University

Date	Job
From April 1989 until now	Takeda Pharmaceutical Company

During August 1994 to July 1995

Visiting scientist, College of Pharmacy, University of Kentucky

Date	Industry Activities
From 2001 to 2003	Osaka Pharmaceutical Manufacturers Association
From 2003 until now	Japan Pharmaceutical Manufacturers Association (JPMA) ICH Q8 JPMA topic deputy leader, Q-IWG Expert

EXHIBIT B

Table 1 - Components and Composition of Formulation A and Formulation B

	Component	Quantity per Tablet (mg)	
		Formulation A	Formulation B
Core Tablet	Metformin HCl membrane coated tablet	1201	1201
Seal Coat	Opadry Clear (YS-1-7006)	9	9
Pioglitazone Coating	Pioglitazone HCl	33.06	33.06
	Hydroxypropyl Cellulose,NF (HPC-SSL)	9	9
	Lactose Monohydrate,NF	30	30
	Polyethylene Glycol 8000,NF	0.45	0.45
	Titanium Dioxide,USP	0.9	0.9
Color Coating	Hydroxypropyl Cellulose,NF (HPC-SSL)		5.32
	Polyethylene Glycol 8000,NF		0.84
	Titanium Dioxide,USP		0.84
Polishing Coat	Candelilla Wax Powder	0.4	0.4
	Total	1283.81	1290.81

Table 2 -Components and Composition of Formulation C

	Component	Quantity per Tablet (mg)
		Formulation C
Core Tablet	Metformin HCl membrane coated tablet	1201
Seal Coat	Opadry Clear (YS-1-7006)	9
Pioglitazone Coating	Pioglitazone HCl	33.06
	Povidone,USP (Kollidon K-30)	3
	Lactose Monohydrate,NF	90
	Poloxamer 188, NF (Lutrol F-68)	15
	Sodium Starch Glycolate, NF (Explotab)	30
Color Coating	Hydroxypropyl Cellulose,NF (HPC-SSL)	5.32
	Polyethylene Glycol 8000,NF	0.84
	Titanium Dioxide,USP	0.84
Polishing Coat	Candelilla Wax Powder	0.4
	Total	1388.46

Table 3

Total impurities (%) of pioglitazone in each formulation after storage at 40°C /75%RH

Formulation	Specification for total impurities	Initial	0.5M	1M	2M	3M
Formulation A	NMT 0.6%	0.18	0.18	0.19	0.16	0.16
Formulation B	NMT 0.6%	0.15	0.14	0.18	0.14	0.18
Formulation C	NMT 0.6%	0.14	0.19	0.29	0.43	0.75

NMT : not more than